THE NORTHERN HOSPITAL

INSULIN-DEXTROSE EUGLYCEMIA

"The Kiss" (Lovers), oil and gold leaf on canvas, 1908- 1909. Gustave Klimt
Österreichische Galerie Belvedere, Vienna.

Inspired by the writer and critic Theophile Gaultier, a great enthusiast of Romanticism, a group of French Artists in the mid to late Nineteenth century began to move away from the Art conventions of the day - Realism and Academic Art. Like the Impressionists, this avant-garde group sought to react against the established norms of the Art world. Instead of Art having to convey, religious, moral or political ideas, this group sought to promote Art as an expression of hidden inner beauty or truths, presented in a manner that was not moralizing but in one that was beautiful - the idea of Art purely for Art's own sake. Beautiful works were produced that evoked feelings, emotions and passions without any moralizing or political messages at all. Often symbols were used that appeared to have no direct relationship to established artistic, biblical or classical icons - often times they were completely enigmatic - a case in point being works like the "Mysterious Sphinx" of Charles van der Stappen. In France the movement became known as "Symbolism". It soon spread to Britain where it became known as "Aestheticism", and was in part an evolutionary progression of the works of the Pre-Raphaelite Brotherhood. In France the Symbolists sought to express deep hidden emotions, feelings and truths, while in Britain, the Aesthetes concentrated more on beauty for its own sake, with an emphasis on form rather than content.

The Symbolist Artists sought to evoke powerful expressions of pure emotion and sensation. Stunning examples are seen in such famous works as Gustave Klimt's, "The Kiss", Franz Von Stuck's "Sin" and Arnold Bocklin's series on the "The Isle of the Dead" and the works in general of Gustave Moreau. As the Romantics of the late Eighteenth century sought to react against the Scientific Enlightenment, so the Symbolists and Aesthetes sought to react against the increasing ugliness of their modern world in the form of the Industrial Revolution. They also sought to react against the strict moralistic codes of Victorian England, yearning a return to the more relaxed ambience of Eighteenth century.

In England, one of the greatest champions of Aestheticism was Oscar Wilde, who became fascinated with the movement during his time as a student at Oxford University. He was ridiculed for his insistence of only having beautiful things around him, but he retained his love of the Aesthetic movement till the day he died. It is said that on his death bed he was looking up at the wallpaper around him. His last recorded words were, "Either that wallpaper goes, or I do!". He would have whole heartedly agreed with the great Pre-Raphaelite, William Morris, "Have ***nothing*** *in your home that you do not know to be useful or believe to be beautiful!"*

With time the Symbolist movement spread from a small group of avant-garde French Artists, to include sculptors, writers, architects and designers in a broad cultural trend that included all of Northern and Western Europe. The movement declined on the death of Oscar Wilde in 1895, but had a powerful hand in the birth of its immediate Artistic successor - the stunning Art Nouveau of the early Twentieth century. The Symbolist and Aesthetic movements taught the world to think outside of the strict convention of the day and to seek out deeper hidden truths. We can apply this beloved philosophy of Oscar Wilde, the Symbolists and the Aesthetes today. In Medicine we should not close our minds to the conventions of the day - but rather open them to new possibilities and perhaps deeper hidden truths. When we consider the case of Insulin our conventions tell us that this is purely a hormone for the physiological control of our glucose metabolism - yet it

appears that there is more to this bio-chemical substance than we realize! By thinking outside of strict convention we see that in very high doses a new property emerges, fractal like, that reveals to us its previously hidden inotropic effects! In patients who take large overdoses of calcium channel blockers or beta blockers, by our usual conventions we face the symbolist vision of Bocklin's "Isle of the Dead" - all conventional therapy may fail to preserve life. But by expanding our minds to deeper hidden truths, we make unconventional use of the hormone Insulin to provide hope for a Symbolist vision of Klimt's "The Kiss" - a strong, beautiful and stunning vision of life.

We find this hidden property of Insulin both beautiful ***and*** *useful.*

"Isle of the Dead", Basel version, oil on canvas, 1880. Arnold Böcklin

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Introduction

Insulin - dextrose euglycemic therapy (or High dose insulin therapy - HDI) is a novel treatment that has been shown to have **positive inotropic** effects in the setting of **calcium channel blocker** overdose and in **beta blocker** overdose.

The important principles of the technique include:

- Insulin must be given in **high doses** to provide the positive inotropic effects to the heart.
- Glucose must be given continuously to prevent hypoglycemia, and the levels carefully monitored.
- Potassium levels must be carefully monitored, as hypokalemia may result.
- Sodium levels must be carefully monitored, in view of the continuous infusion of dextrose.

HDI has been found to be superior to conventional therapies and should be initiated early as soon as cardiogenic shock occurs.

As experience is limited dosing should be guided by a clinical Toxicologist.

Mechanism

The mechanism of insulin's inotropic action is not currently well understood, but is probably due to a number of factors.

Intracellular transport of glucose in cardiac and skeletal muscle is greatly enhanced by insulin and has been implicated as an essential component of its inotropic action, via a number of calcium mediated effects.

Additionally stressed myocardium primarily uses glucose as its preferred energy substrate, (while preferring fatty acid oxidation under normal conditions).

Catecholamines can increase blood pressure and heart rate, but they also increase **SVR** which may result in decreases in cardiac output and perfusion of vascular beds. The increased myocardial oxygen demand that results from catecholamines and vasopressors may be also be detrimental in the setting of hypotension and decreased coronary perfusion.

Insulin on the other hand, is a vasodilator of the systemic, coronary, and pulmonary vasculature. These vasodilatory effects are due to enhancement of endothelial nitric oxide synthase (eNOS) activity by its effects on PI3K (a major insulin intracellular signaling

pathway). Insulin thus can enhance microvascular perfusion. It also enhances myocardial contractility without increasing myocardial oxygen demand.

Indications

Indications are:

1. Calcium channel blocker overdose with significant hemodynamic compromise not responding to initial resuscitation. It should be instituted sooner in these cases rather than later.

2. Beta blocker overdose with significant hemodynamic compromise not responding to initial resuscitation. It should be instituted sooner in these cases rather than later.

Contraindications

There are none when this treatment is required.

Procedure

Commence therapy by giving:

- **50 mls of 50 % dextrose (i.e 25 grams of dextrose) IV**

Followed by:

- **1 unit/kg IV actrapid.**

Then commence insulin and dextrose infusion:

Insulin infusion

- **1 U/kg of actrapid (short acting insulin) per hour.**

  Under the direction of a Clinical Toxicologist this may be increased to 10 U/kg of actrapid per hour if needed.

  Escalation regimens are not standardized, but as a general guide:

  - ♥ **Increase by 1-2 U/kg/hr every 30-45 minutes depending on response.** (*personal communication Dr Zeff Koutsogiannis, October 2015*).

Dextrose infusion

- **Give 50% glucose via a central line (a femoral vein can be used) commencing at 25 grams per hour, (i.e. 50 mls per hour).**

- **The dextrose infusion is titrated to maintain euglycemia**

Note that by using the 50% concentration, the complication of hyponatremia is minimized when compared to using 5 or 10 % solutions where much larger volumes would be required. This will also reduce the risk of excessive volume loading.

Biochemical Monitoring:

It will be essential to monitor:

1. BSL:
    - Bedside **BSL** 10 minutely initially.
    - Check BSL every 30 -60 minutes once the insulin dose is stable
2. Electrolyte levels, **at least hourly** initially.
    - Look for **hypokalemia** because of the large doses of insulin and glucose being delivered and replace as necessary.

      Aim to maintain serum potassium in the range of 3.0 - 3.5 mmol/L as the total body stores are not depleted, and potassium will move back to the extracellular compartments once insulin is discontinued.
    - Look for **hyponatremia** with prolonged dextrose infusions.

      Using 50% dextrose solutions will minimize the risk of hyponatremia as well as excessive volume overloading.

End Points:

Therapy is weaned as cardiovascular instability resolves.

Aim for a systolic blood pressure of at least 90 mmHg.

Dextrose supplementation may be required for up to 24 hour post-insulin discontinuation due to elevated insulin concentrations.

References

1. Calcium channel blocker overdose in L Murray et al. Toxicology Handbook 3rd 2015.

3. Insulin High Dose (Insulin-Dextrose Euglycemia) in L Murray et al. Toxicology Handbook 3rd ed 2015.

3. Engerbretsen K.M et al. High-dose insulin therapy in beta-blocker and calcium channel blocker poisoning. Clinical Toxicology (2011) 49, 277- 283.

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